

Nuisance parameter based sample size re-estimation incorporating prior information

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Abstract

Prior information is often incorporated informally when planning a clinical trial. Here, we present an approach on how to incorporate prior information, such as data from historical clinical trials, into the nuisance parameter based sample size re-estimation in a design with an internal pilot study. We focus on trials with continuous endpoints in which the outcome variance is the nuisance parameter. For planning and analyzing the trial frequentist methods are considered. Moreover, the external information on the variance are summarized by the Bayesian meta-analytic-predictive approach. To incorporate external information into the sample size re-estimation, we propose to update the MAP prior based on the results of the internal pilot study and to re-estimate the sample size using a Bayes estimator from the posterior. By means of a simulation study, we compare the operating characteristics such as power and sample size distribution of the proposed procedure with the traditional sample size re-estimation approach which uses the pooled variance estimator. The simulation study shows that, if no prior data conflict is present, incorporating external information into the sample size re-estimation improves the operating characteristics compared to the traditional approach. In the case of a prior data conflict, that is when the variance of the ongoing clinical trial is unequal to the prior location, the performance of the traditional sample size re-estimation procedure is in general superior, even when the prior information is robustified. When considering to include prior information in sample size re-estimation, the potential gains should be balanced against the risks.

Keywords: sample size re-estimation, meta-analysis, meta-analytic-predictive priors, nuisance parameter, internal pilot study

1 Introduction

Sample size determination is an essential part when planning clinical trials since an adequate sample size assures that the objectives of the clinical trial can be assessed with

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high statistical confidence. The conduct of clinical trials with inappropriate sample sizes is often considered unethical.^[1] In clinical trials with a continuous outcome variable, the sample size planning is often based on the assumption of normal data. In this case, the sample size is affected by the outcome variance and the assumed treatment effect size as well as the type I and type II error rates. When planning the sample size, the treatment effect size is generally determined based on clinical relevancy and the type I and type II error rates are selected from a set of agreed upon values. However, the outcome variance is usually unknown and determining it to calculate the sample size has been discussed extensively in literature. If historical trials with designs similar to the planned trial are available, the variance for the sample size formula can be estimated from the historical trials.^[2,3,4] Others have also proposed to additionally consider the variability of such variance estimators in the sample size calculation.^[5] Another possibility to obtain an estimate of the outcome variance is from a pilot study. Pilot studies can either be internal or external and the difference being that internal pilot studies are part of the main clinical trial or and external pilot studies are a separate entity.^[6] The variance estimate from an external pilot study can be considered for the sample size planning of a clinical trial and to adjust for the uncertainty of the estimate from the pilot study, it has been proposed to consider upper confidence limits of the variance instead of the variance estimate.^[7,8,9] The mentioned approaches all aim to plan the sample size of a new clinical trial based on external information about the variance. Naturally, there is no guarantee that the outcome variance of a clinical trial corresponds to the estimate obtained from external information. For situations in which information on the variance is uncertain, it has been proposed to include an internal pilot study into the design of a clinical trial and to re-estimated the outcome variance (or nuisance parameters in general), and thus the sample size of the ongoing clinical trial, based on the results of the internal pilot study.^[6] Nuisance parameter based sample size re-estimation in clinical trials has been studied extensively and we refer to reviews for a detailed recapitulation.^[10,11,12]

In this manuscript we focus on two-arm parallel group superiority trials with normally distributed endpoints planned and analyzed using frequentist methods. We assume that the clinical trial design includes an internal pilot study with a nuisance parameter based sample size re-estimation and that variance estimates from several similar historical clinical trials are available when planning the new clinical trial. The information about the variance from the historical clinical trials are then summarized by a meta-analysis using a Bayesian hierarchical model and the predicted variance of a new clinical trial is formalized as an meta-analytic-predictive (MAP) prior.^[4] We study several methods to incorporate the prior information into the unblinded sample size re-estimation and assess the performance characteristics of the respective sample size re-estimation procedures; these are the power and the distribution of the final sample size, in a Monte-Carlo simulation study. We focus on re-estimating the sample size such that the clinical trials maintains a pre-specified power. Our motivation for primarily focusing on incorporating information into the sample size re-estimation based on unblinded data instead of blinded data are of computational nature. We then elaborate on why the findings for unblinded data are qualitatively the same as for incorporating information into the sample size re-estimation based on blinded data. Incorporating external information in form of a prior distribution into nuisance parameter based sample size re-estimation has already been proposed for binomial data in the early 1990s but not studied intensively.^[13] More recently, Hartley

introduced a “mostly Bayesian” approach to blinded sample size re-estimation for normal data.^[14]

This manuscript is structured as follows. In Section 2 we elaborate the statistical model and recapitulate MAP priors as well as how to incorporate external information into the sample size planning. In Section 3 we propose several procedures for incorporating external information into the sample size re-estimation. Clinical trial examples are discussed in Section 4. The performance characteristics of the introduced sample size re-estimation procedures incorporating external data are studied in Section 5. In Section 6 we discuss how prior information can be incorporated into the sample size re-estimation with blinded data and why the performance of the resulting procedures are qualitatively identical to the performance of the procedures based on unblinded data. We conclude by discussing the findings with particular emphasis on the inappropriateness of incorporating prior information into the nuisance parameter based sample size re-estimation.

2 Statistical model and meta-analytic-predictive priors

This section is split into three parts. In the first part we outline the statistical model considered in this manuscript and the classical frequentist approach of sample size planning. In the second part we recapitulate MAP priors. Several approaches for incorporating prior information into frequentist sample size planning are discussed in the third part.

2.1 Statistical model

We consider a two-arm parallel group superiority trial with normally distributed endpoints. More precisely, let X_{ij} be the random variable modeling observation $j = 1, \dots, n_i$ in group $i = T, C$. Here, $i = T$ indicates the treatment group and $i = C$ the control group. The randomization ratio is given by $k = n_C/n_T$ and the total sample size is given by $n = n_T + n_C$. The random variables are independently normally distributed given the group mean μ_i and the variance σ^2 , i.e.

$$X_{ij}|\mu_i, \sigma^2 \sim \mathcal{N}(\mu_i, \sigma^2).$$

Larger values of μ_i , $i = T, C$, are considered to be more desirable. We focus on the frequentist hypothesis testing problem

$$H_0 : \mu_T \leq \mu_C \quad \text{vs.} \quad H_1 : \mu_T > \mu_C.$$

The most common test for the hypothesis H_0 is the two-sample Student’s t -test with test statistic

$$T = \frac{\bar{X}_T - \bar{X}_C}{\hat{\sigma} \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}}.$$

The sample standard deviation $\hat{\sigma}$ is the square root of the pooled sample variance. The null hypothesis H_0 would be rejected if the test statistic T exceeds $t_{n-2, 1-\alpha}$, the $(1 - \alpha)$ -quantile of a t -distribution with $n - 2$ degrees of freedom. Under the alternative hypothesis

H_1 , the test statistic T follows a noncentral t -distribution with $n - 2$ degrees of freedom and noncentrality parameter

$$\lambda = \frac{\delta}{\sigma \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}} = \frac{\sqrt{nk} \delta}{k + 1} \frac{1}{\sigma}.$$

Thus, the power of Student's t -test can be expressed as a function $B(n, \sigma^2, \delta)$ of the sample size n , the variance σ^2 , and the effect size δ , i.e.

$$B(n, \sigma^2, \delta) = \mathbb{P}(T \geq t_{n-2, 1-\alpha}) = 1 - F_{nct}(t_{n-2, 1-\alpha}; \lambda, n-2)$$

with $F_{nct}(\cdot; \lambda, \nu)$ the cumulative distribution function of a noncentral t -distribution with noncentrality parameter λ and ν degrees of freedom. The total sample size n to test the hypothesis H_0 with a prespecified nominal power of $1 - \beta$ is given by

$$n = \min \left\{ \tilde{n} \in \mathbb{N} : F_{nct}(t_{\tilde{n}-2, 1-\alpha}; \lambda^*, \tilde{n}-2) \leq \beta; \quad \lambda^* = \sqrt{\tilde{n}k} \frac{\delta^*}{\sigma(k+1)} \right\}. \quad (1)$$

Here, $\delta^* > 0$ is the assumed effect size under the alternative. Especially for large sample sizes closed form approximations of the above sample size formula based on normal quantiles or quantiles of Student's t -distribution exist and are commonly applied in practice.

2.2 Meta-analytic-predictive priors

Planning the sample size of a trial based on Formula (1) requires knowledge about the variance σ^2 . In practice, information about the variance σ^2 is often gathered from historical studies. Schmidli et al. formalized information gathering for nuisance parameters based on the meta-analytic-predictive (MAP) approach.^[4] In the following, we give a brief introduction to the MAP approach for variances. The idea is to perform a random effects meta-analysis using a normal Bayesian hierarchical model for the logarithm of the variance. The resulting posterior predictive distribution for the variance is called MAP prior and is used to predict the variance of a new clinical trial. In detail, let $j = 1, \dots, J$ be the index for J historical clinical trials and let $\hat{\sigma}_j^2$ be the sample variance and ν_j the respective degrees of freedom. The unknown true variance of trial $j = 1, \dots, J$ is denoted by σ_j^2 . Considering that we are focusing on clinical trials with normal data, we assume that the sample variances follow a χ^2 -distribution in the sense

$$\frac{\nu_j}{\sigma_j^2} \hat{\sigma}_j^2 \Big| \sigma_j^2 \sim \chi_{\nu_j}^2.$$

We note that the χ^2 -distribution is a special case of the Gamma distribution and it follows that

$$\hat{\sigma}_j^2 \Big| \sigma_j^2 \sim \text{Gamma} \left(0.5\nu_j, 0.5 \frac{\nu_j}{\sigma_j^2} \right).$$

A random variable following a Gamma distribution with shape parameter a and rate parameter b , $\text{Gamma}(a, b)$, has mean a/b and variance a/b^2 . To gather information about the variance σ_{new}^2 of a new, to be planned clinical trial from the variances of historical

clinical trial, the variance σ_{new}^2 and the variances σ_j^2 of historical clinical trials have to be linked. As it is common in random effects meta-analyses, we assume that the variances origin from the sample distribution by assuming that the log-transformed variances $\theta_{new} = \log(\sigma_{new}^2)$, $\theta_1 = \log(\sigma_1^2)$, \dots , $\theta_J = \log(\sigma_J^2)$ follow a normal distribution,

$$\theta_{new}, \theta_1, \dots, \theta_J \sim \mathcal{N}(\mu, \tau^2).$$

The random effects meta-analysis can be performed using a Bayesian hierarchical model. Thereto, prior distributions for the mean μ and the between-trial standard deviation τ have to be selected. Common choices are weakly informed priors such as a normal distribution with a large variance for the mean and a half-normal distribution for the standard deviation.^[4] The posterior density $p(\mu, \tau, \theta_{new} | \hat{\sigma}_1^2, \dots, \hat{\sigma}_J^2)$ cannot be calculated analytically. However, through Markov chain Monte Carlo (MCMC) computations random samples of the parameter vector $(\mu, \tau, \theta_{new})$ can be generated. The random numbers for θ_{new} can then be transformed to obtain random numbers for the posterior predictive distribution of the variance of a new trial σ_{new}^2 . The posterior predictive distribution of σ_{new}^2 is the MAP prior for the variance. The MAP prior for the variance does in general not have a closed form expression but, as every prior distribution, it can be approximated by a mixture of conjugated priors.^[15] For the sake of convenience, the prior of the precision $\omega = 1/\sigma^2$, and not the prior of the variance σ^2 , is approximated by a mixture of conjugated priors. For a normal model, the conjugated prior of the precision is the Gamma distribution. Therefore, in this manuscript we assume that the prior distribution for the precision $\omega = 1/\sigma^2$ is a mixture of Gamma distributions

$$\omega \sim \sum_{l=1}^L w_l \text{Gamma}(a_l, b_l).$$

The parameters w_l , a_l , and b_l are obtained by calculating the maximum-likelihood estimators from the MCMC random sample of $1/\exp(\theta_{new})$. For details on the methodological background of the MAP approach and its use to summarize historical information on the variance, we refer to Schmidli et al.^[4,16] Since ω follows a mixture of Gamma distributions, the variance σ^2 follows a mixture of inverse Gamma distributions with the same weights, shape parameters, and rate parameters. An inverse Gamma distributed random variable with shape parameter a and rate parameter b , $\text{InvGamma}(a, b)$, has mean $b/(a-1)$ and variance $b^2/((a-1)^2(a-2))$.

The MAP prior for the variance might mismatch the variance observed in a new clinical trial, i.e. a prior data conflict can be present. Schmidli et al. introduced a robustified version of MAP priors which aims to mitigate the risk of a prior data conflict.^[16] We briefly recapitulate their robustification of MAP priors. Thereto, let $p_{MAP}(\cdot)$ be an MAP prior and let $p_V(\cdot)$ be a vague conjugate prior. Moreover, let w_R be the prior probability of a prior data conflict. Then, a robustified MAP prior with density $p_{rMAP}(\cdot)$ is the mixture distribution of the MAP prior and the vague conjugate prior with mixture probability w_R , that is

$$p_{rMAP}(x) = w_R p_V(x) + (1 - w_R) p_{MAP}(x).$$

2.3 Sample size planning based on prior information on the nuisance parameter

In the following we outline how prior information on the nuisance parameter can be incorporated into the frequentist sample size calculation of a clinical trial. The methods for including prior information into the nuisance parameter based sample size re-estimation which we will present in the next section follow the sample principles. To plan the sample size n of a new trial based on the MAP prior $p_{\sigma^2}(\cdot)$ of the variance σ^2 , a Bayes estimator of σ^2 can be plugged into Formula (1).^[4] There are various ways of defining a Bayes estimator, in this sense, Bayes estimators are not unique.^[17] Here, we focus on the mean $\hat{\sigma}_{mean}^2$ and the median $\hat{\sigma}_{med}^2$ of the MAP prior which minimize the squared error risk and the absolute deviation, respectively. The sample size can also be planned based on prior information on the standard deviation σ or on the precision $\omega = 1/\sigma^2$. However, if the Bayes estimator is not transformation invariant, the resulting sample size will differ from the planning based on prior information on the variance. When the sample size is determined based on a location parameter of the MAP prior, the uncertainty of the prior information is not considered in the planning process. Alternative approaches which consider the variability of the prior information can either choose percentiles of the MAP prior in Equation (1) or base the sample size on the expected power. The unconditional power concerning σ^2 is the function

$$\tilde{B}(n_1, \delta) = \int B(n, x, \delta) p_{\sigma^2}(x) dx.$$

The total sample size n for testing the hypothesis H_0 which is then defined by

$$n = \min \left\{ \tilde{n} \in \mathbb{N} : \tilde{B}(\tilde{n}, \delta^*) \geq 1 - \beta \right\}. \quad (2)$$

It is worth emphasizing that the sample size obtained from the expected power is in general different to the sample size obtained with Formula (1).

3 Nuisance parameter based sample size re-estimation using MAP priors

In this section we briefly summarize the general idea of nuisance parameter based sample size re-estimation in designs with internal pilot study and then propose methods which incorporate prior information on the variance in the form of MAP priors into the sample size re-estimation. As the name implies, in nuisance parameter based sample size re-estimation the sample size is altered after the internal pilot study based on an estimate of the nuisance parameter. The estimation of the nuisance parameter can either be done based on blinded or unblinded data. From a regulatory perspective it must be addressed whether and how the blindness during the sample size re-estimation was maintained, confer Section 4.4 of ICH guideline E9.^[18] Other regulatory publications recommend blinded sample size re-estimation whenever possible, such as a reflection paper by the Committee for Medicinal Products for Human Use (CHMP).^[19] The recommended method for sample size re-estimation in two-arm parallel group trials with continuous data is the blinded one-sample variance estimator which estimates the unknown variance by the sample variance of the blinded data.^[20,21,22] The one-sample variance estimator results in a sample

size re-estimation procedure which meets the power and controls the type I error rate for practically relevant internal pilot study sizes. Although the one-sample variance estimator is the recommended method for nuisance parameter based sample size re-estimation, we first introduce the sample size re-estimation incorporating prior information for unblinded data. The primary reason is that unblinding of the internal pilot study leads to closed form expressions for the sample size re-estimation incorporating external information. We will show in Section 6 that the performance of the sample size re-estimation procedure incorporating prior information based on blinded data is qualitatively the same as for the procedure relying on unblinded data. Altering the sample size of an ongoing clinical trial based on unblinded data from an internal pilot study has first been proposed by Wittes et al.^[6] In detail, the idea is to perform an internal pilot study of size n_1 , with n_{1T} and n_{1C} denoting the group specific sample sizes within the internal pilot study. After the outcome measure of the n_1 patients is obtained, the pooled variances $\hat{\sigma}_{1,pool}^2$ from the unblinded data is calculated. The sample size is then re-estimated based on the estimate $\hat{\sigma}_{1,pool}^2$ using Equation (1). Let \hat{n}_{reest} denote the re-estimated sample size. Here, we consider the final sample size of the clinical trial to be the maximum of the re-estimated sample size and the internal pilot study sample size, i.e. $\hat{n}_{final} = \max\{\hat{n}_{reest}, n_1\}$.^[23] Alternatively, the final sample size can be set to be the maximum of the initially planned sample size and the re-estimated sample size in which case the sample size re-estimation would not be able to reduce the initially set sample size.^[6] In the case of constrained resources it can also be reasonable to additionally include an upper limit for the final sample size.^[13] Sample size re-estimation based on the pooled sample variance is able to adjust for a misspecified variance during the planning of the clinical trial if the internal pilot study is reasonably sized.^[6,23,24] This sample size re-estimation approach inflates the type I error rate and due to the unblinding might trigger the need of an Independent Data Monitoring Committee (IDMC) to preserve the blindness of the study personnel. It is worth mentioning that the type I error rate inflation can be minimized when a bias correction is applied to the variance estimator in the test statistic at the end of the trial.^[25] We do not apply this bias correction here because it qualitatively does not change the performance of the sample size re-estimation procedure incorporating prior information.

When the sample size of a clinical trial is planned utilizing prior information or in general when prior information on the nuisance parameter is available, it seems intuitive to incorporate said prior information into the sample size re-estimation. We propose to incorporate prior information on the nuisance parameter into the sample size re-estimation by updating the prior using the data from the internal pilot study and then re-calculating the sample size with (1) based on a Bayes estimator of the variance obtained from the posterior distribution. In more detail, let X_{ij} be the random variable modeling observation $j = 1, \dots, n_{1i}$ in group $i = T, C$ after the internal pilot study and let $\omega = 1/\sigma^2$ be the precision. The prior information on the parameters (μ_T, μ_C, ω) is characterized by the prior density $p(\mu_T, \mu_C, \omega)$. Thus, for the posterior density after the internal pilot study holds

$$p(\mu_T, \mu_C, \omega | \bar{X}_{1T}, \bar{X}_{1C}, \hat{\sigma}_{1,pool}^2) \propto p(\bar{X}_{1T}, \bar{X}_{1C}, \hat{\sigma}_{1,pool}^2 | \mu_T, \mu_C, \omega) p(\mu_T, \mu_C, \omega).$$

Here, \bar{X}_{1T} , \bar{X}_{1C} , and $\hat{\sigma}_{1,pool}^2$ denote the mean in the treatment group, the mean in the control group, and the pooled sample variance, respectively, obtained from the unblinded data of the internal pilot study. In this manuscript we focus on the specific case of an

improper uniform prior for the means which is a-prior independent of the prior for the precision,

$$\begin{aligned} p(\mu_T, \mu_C) &= p(\mu_T)p(\mu_C) = 1, \\ p(\mu_T, \mu_C, \omega) &= p(\mu_T, \mu_C)p(\omega). \end{aligned}$$

As mentioned in the previous section, we assume that the precision ω has a mixture of Gamma distributions as the prior. In the assumed model, this prior distribution is a conjugate prior and thus the marginal posterior for the precision is again a mixture of Gamma distributions,^[26]

$$\omega \mid \bar{X}_{1T}, \bar{X}_{1C}, \hat{\sigma}_{1,pool}^2 \sim \sum_{l=1}^L w_l^* \text{Gamma} \left(a_l + \frac{n_1 - 2}{2}, b_l + \frac{n_1 - 2}{2} \hat{\sigma}_{1,pool}^2 \right).$$

The updated weights w_l^* are given by

$$w_l^* = \frac{r_l}{\sum_{l=1}^L r_l}$$

where the single components r_l are calculated by

$$r_l = w_l \frac{\Gamma(a_l + 0.5(n_1 - 2))}{(b_l + 0.5(n_1 - 2) \hat{\sigma}_{1,pool}^2)^{a_l + 0.5(n_1 - 2)}} \frac{b_l^{a_l}}{\Gamma(a_l)}.$$

The posterior for the variance σ^2 follows therefore a mixture of inverse Gamma distributions. We denote the mean and the median of the posteriors distribution of σ^2 as $\hat{\sigma}_{1,mean}^2$ and $\hat{\sigma}_{1,med}^2$, respectively. The mean $\hat{\sigma}_{1,mean}^2$ of the posterior distribution is the weighted mean of inverse Gamma distributions,

$$\hat{\sigma}_{1,mean}^2 = \sum_{l=1}^L w_l^* \frac{b_l + \hat{\sigma}_{1,pool}^2(n_1 - 2)/2}{a_l + (n_1 - 2)/2 - 1}$$

The median of an inverse Gamma distribution and the median of a mixture of inverse Gamma distributions do not have closed form expressions and must be calculated iteratively. The re-estimated sample size \hat{n}_{reest} is obtained through (1) by plugging in a Bayes estimator for the variance. Analogously to the planning of a clinical trial, the sample size can also be determined by means of the expected power, confer (2), or by plugging in percentiles of the posteriors distribution into (1).

4 Clinical trial examples

In this section we discuss two examples in which we gather information on the variance from historical clinical trials and predict the variance of a new trial using the meta-analytic-predictive approach. We then study how the prior information about the variance affects the re-estimated sample size when incorporated into the sample size re-estimation.

4.1 St John’s wort for major depression

The first example focuses on the use of St John’s wort for major depression. Linde et al. published a meta-analysis summarizing the effects of St John’s wort for major depression for a variety of endpoints.^[27] Here, we focus on the Hamilton Rating Scale for Depression (HAMD) score after four weeks of treatment.^[28] In Analysis 2.3 of their review, Linde et al. summarize the results of eleven trials comparing hypericum (St John’s wort) versus placebo. From the reported results we obtain a pooled variance estimator and the respective number of degrees of freedom for each trial. The MAP prior for the precision and, thus, the variance is obtained through a Bayesian meta-analysis of the sample variances as outlined in Section 2.2. The MAP prior of the precision $\omega = 1/\sigma^2$ can be approximated by the following Gamma mixture distribution

$$0.16 \text{ Gamma}(4.6, 140.4) + 0.84 \text{ Gamma}(18.2, 689.3).$$

The effective prior sample size can be calculated as the product of the degrees of freedom of the historical trials multiplied by the ratio of the predictive variance assuming no between-trial heterogeneity and the predictive variance accounted for between-trial heterogeneity.^[29] Here, this leads to an effective prior sample size of $ESS = 24$. Table 1 list characteristics of the MAP priors. Table 1 highlights that the prior information on the

Table 1: Summaries of the MAP priors for the variance σ^2 , the standard deviation σ , and the precision ω .

Parameter	Mean	SD	Median	2.5% quantile	97.5% quantile
σ^2	39.56	12.56	37.93	21.11	68.52
σ	6.22	0.93	6.16	4.59	8.27
ω	0.0276	0.0097	0.0267	0.0146	0.0474

outcome variance is quite uncertain. In the following we study how the prior information affects the sample size when incorporated into the sample size re-estimation. Thereto, we assume internal pilot study sizes of $n_1 = 25, 75, 125$ and that the sample size re-estimation is performed with an assumed effect of $\delta^* = 2.515$ which corresponds to a standardized effect of about 0.4 for a variance of $\sigma^2 = 39.56$. For this parameter combination, the sample size in a fixed sample design would be $n = 198$. In Figure 1 the re-estimated sample size is plotted against the pooled sample variance $\hat{\sigma}_{pool}^2$ obtained from the internal pilot study. Figure 1 shows that the re-estimated sample sizes based on the Bayes estimators, that are the posterior mean and the posterior median, are not increasing as step as the re-estimated sample size based on the pooled sample variance. Moreover, the difference between the re-estimated sample sizes with and without incorporated prior information decreases as the internal pilot study sample size n_1 increases. In other words, the influence of the prior information on the re-estimated sample size decreases as the internal pilot study sample size increases.

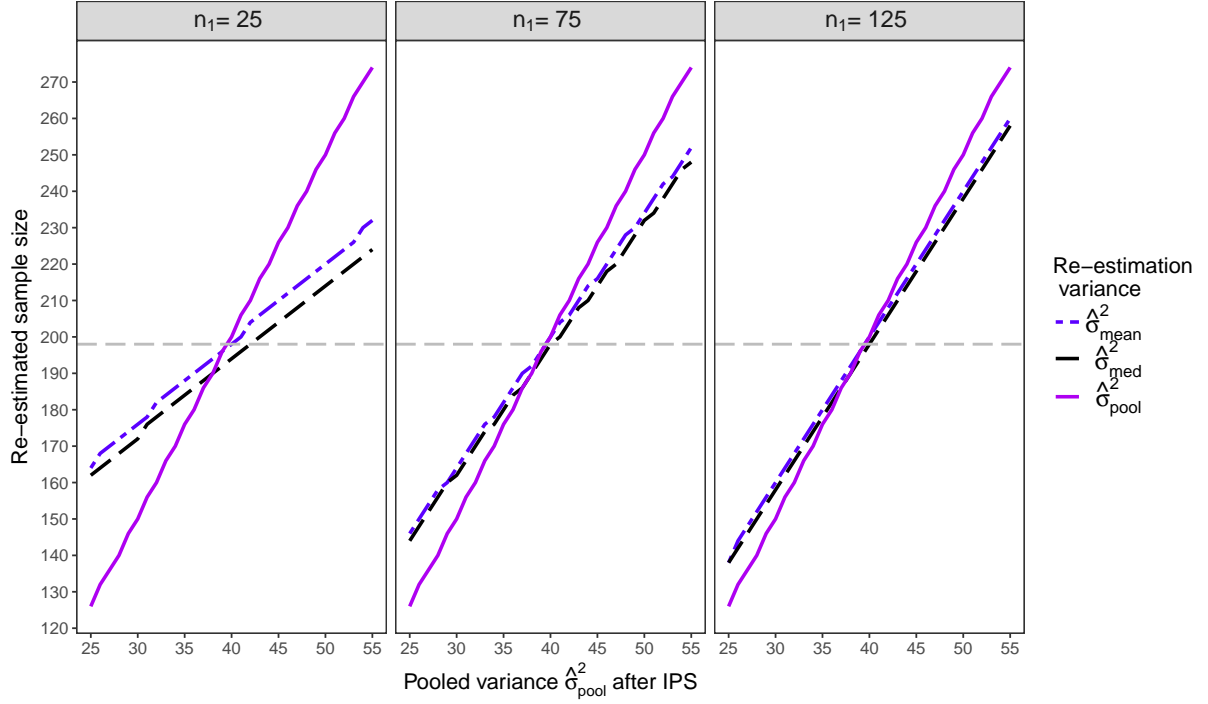


Figure 1: Re-estimated sample size for the unblinded sample size re-estimation based on the pooled variance $\hat{\sigma}_{pool}^2$ and for the sample size re-estimation incorporating prior information based on the posterior mean $\hat{\sigma}_{mean}^2$ and on the posterior median $\hat{\sigma}_{med}^2$, respectively.

4.2 Interventions for controlling blood pressure

To improve the blood pressure control of hypertensive patients a variety of interventions such as self-monitoring, patient education, health care provider education, appointment reminders, etc. have been proposed. In a meta-analysis, Glynn et al. summarized the available literature on the effect of various interventions on the blood pressure.^[30] In our example, we focus on the reported results about the systolic blood pressure for patients who self-monitored their blood pressure, confer Analysis 1.1 in Glynn et al.^[30] With the reported sample variances, we proceed as in the previous example: we calculate a pooled variance for each study and then perform an Bayesian meta-analysis for the sample variances. The mixture of Gamma distributions

$$0.29 \text{ Gamma}(10.28, 2298.63) + 0.71 \text{ Gamma}(38.46, 9366.28).$$

approximates the MAP prior of the precision $\omega = 1/\sigma^2$. The effective sample size is $ESS = 41$. Summary statistics of the MAP priors of the variance, standard deviation, and the precision are listed in Table 2. Analogously to the first example, we study how the prior affects the re-estimated sample size. As before, the internal pilot study sample sizes are assumed to be $n_1 = 25, 75, 125$ and the assumed effect is again chosen such that a standardized effect of 0.4 is obtained for the prior mean of the variance, hence $\delta^* = 6.343$. The sample size in a fixed sample design would be $n = 198$. The results shown in Figure 2 are qualitatively the same as in Figure 1. However, since the prior effective sample size is larger in the second example, the difference between the re-estimated sample sizes from the methods with and without incorporated prior information is larger, too.

Table 2: Summaries of the MAP priors for the variance σ^2 , the standard deviation σ , and the precision ω .

Parameter	Mean	SD	Median	2.5% quantile	97.5% quantile
σ^2	251.47	58.24	244.7	157.8	385.7
σ	15.76	1.76	15.64	12.56	19.64
ω	0.0042	0.00094	0.0041	0.0026	0.0063

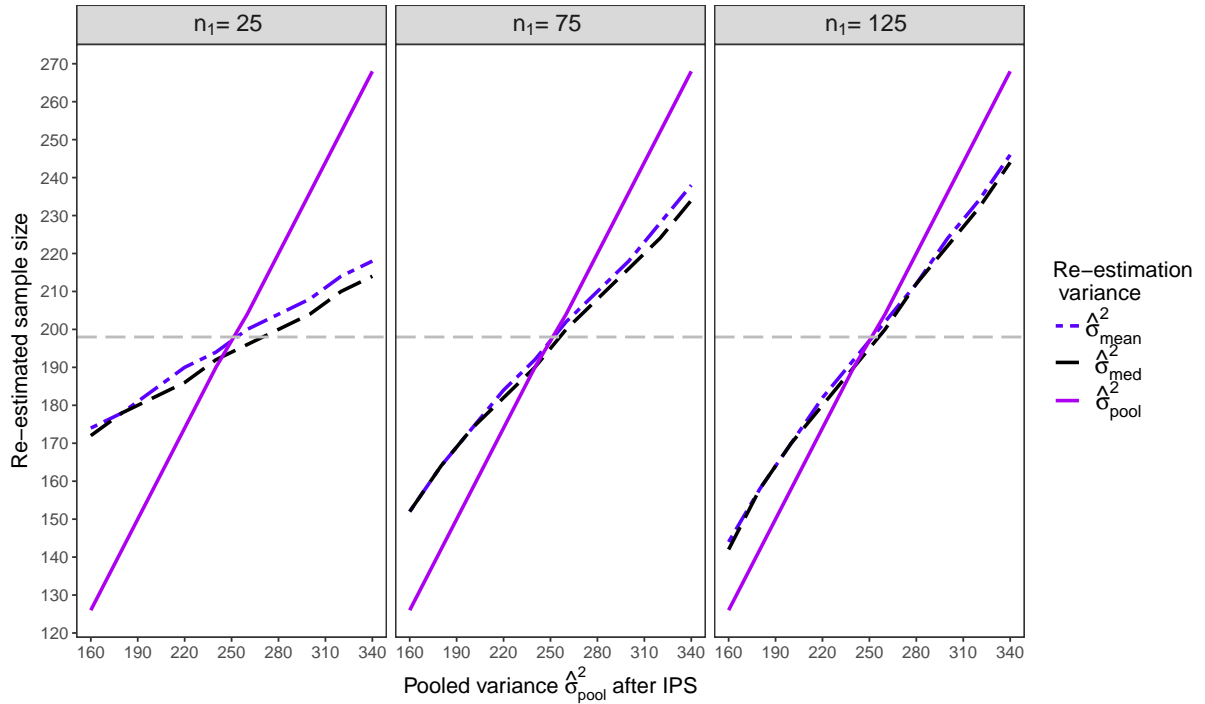


Figure 2: Re-estimated sample size for the unblinded sample size re-estimation based on the pooled variance $\hat{\sigma}_{pool}^2$ and for the sample size re-estimation incorporating prior information based on the posterior mean $\hat{\sigma}_{mean}^2$ and on the posterior median $\hat{\sigma}_{med}^2$, respectively.

5 Performance of the proposed sample size re-estimation procedure

The most important operating characteristic of a sample size re-estimation procedure is whether the test at the end of the study meets the target power under the condition that the type I error rate is controlled under the null hypothesis. Further operating characteristics are the distribution of the final sample size and the type I error rate. In the following we assess the performance of the t-test at the end of the study after the sample size has been altered mid-study using the re-estimation procedure which incorporates prior information. The performance assessment is conducted by means of a Monte Carlo simulation study. Particular emphasis will be placed on the comparison of the proposed sample size re-estimation procedure with the sample size re-estimation approach based on the pooled

variance. Several methods for determining the sample size given a prior distribution were discussed in the previous section. During the presentation of the results of the simulation study we restrict ourselves to sample sizes re-estimated based on the Bayes estimators $\hat{\sigma}_{mean}^2$ and $\hat{\sigma}_{med}^2$ and do not include sample size re-estimation based on the expected power concerning σ^2 or on quantiles of the posterior distribution. The performance is qualitatively the same and therefore not presented here. The simulation study is split into three parts. We start by considering an ideal setting in which the prior information is correct, in other words no prior data conflict exists in the sense that the prior mean corresponds to the true variance of the ongoing clinical trial. Afterwards, we study the performance of the sample size re-estimation procedure for a prior data conflict that is when the prior mean is unequal to the true variance of the ongoing clinical trial. We conclude with scenarios which include a prior data conflict but in which the prior distribution was also robustified. Throughout this section, we select a Gamma distribution, not a mixture of Gamma distributions, as the MAP prior for the precision ω . This simplified setting is already sufficient to highlight the main characteristics of sample size re-estimation procedure incorporating prior information while not artificially increasing the number of parameters. Moreover, the effective sample size can be illustrated easily for a Gamma distribution. The effective sample size for a Gamma distribution with shape parameter a and rate parameter b is given by $ESS = 2a$. Table 3 lists the parameters considered in the simulation study. As

Table 3: Scenarios for the Monte Carlo simulation study.

Parameter	Value
One-sided significance level α	0.025
Target power $1 - \beta$	0.8
Margin δ^* in the alternative	0.5
True variance σ^2	1
Internal pilot study size n_1	10, 20, ..., 100
Sample size ratio k	1
Expected value of prior $p_{\sigma^2}(\cdot)$ (no prior conflict)	1
Expected value of prior $p_{\sigma^2}(\cdot)$ (prior conflict)	0.49
Effective sample size ESS of prior $p_{\sigma^2}(\cdot)$	6, 25, 50

listed in Table 3, the true variance of the normally distributed data is $\sigma^2 = 1$. We assume a mean difference in the alternative of $\delta^* = 0.5$ which requires a fixed sample design sample size of $n = 128$ to obtain a power of $1 - \beta = 0.8$. Moreover, as Table 3 highlights, during the simulation study particular emphasis is put on the performance of the sample size re-estimation procedure when the internal pilot study sample size n_1 and the effective sample size change. The shape parameter a and rate parameter b of the prior density $p_{\sigma^2}(\cdot)$ are chosen based on the effective sample size ESS and the expected value of the prior distribution. The shape parameter is half of the effective sample size: $a = ESS/2$. Let σ_{mean}^2 denote the expected value of the prior distribution of the variance. Since the prior of the variance has an inverse Gamma distribution, the expected value is given by $\sigma_{mean}^2 = b/(a - 1)$. Thus, the rate parameter is determined to be $b = \sigma_{mean}^2(ESS/2 - 1)$. The expected value σ_{mean}^2 of the prior distribution is set to one to model the settings with

no prior data conflict. On the other hand, to model a prior data conflict, the expected value of the prior distribution is set to $\sigma_{mean}^2 = 0.49$. Each simulated power in this section is based on 50 000 Monte Carlo replications which corresponds to a simulation error of less than 0.0018 for a simulated power of 0.8. In the following the results of the Monte Carlo simulation study are presented for the scenarios without prior data conflict listed in Table 3. Figure 3 plots the power of Student's t -test against the internal pilot study sample size n_1 for the different sample size re-estimation procedures. Figure 3 shows, if no prior

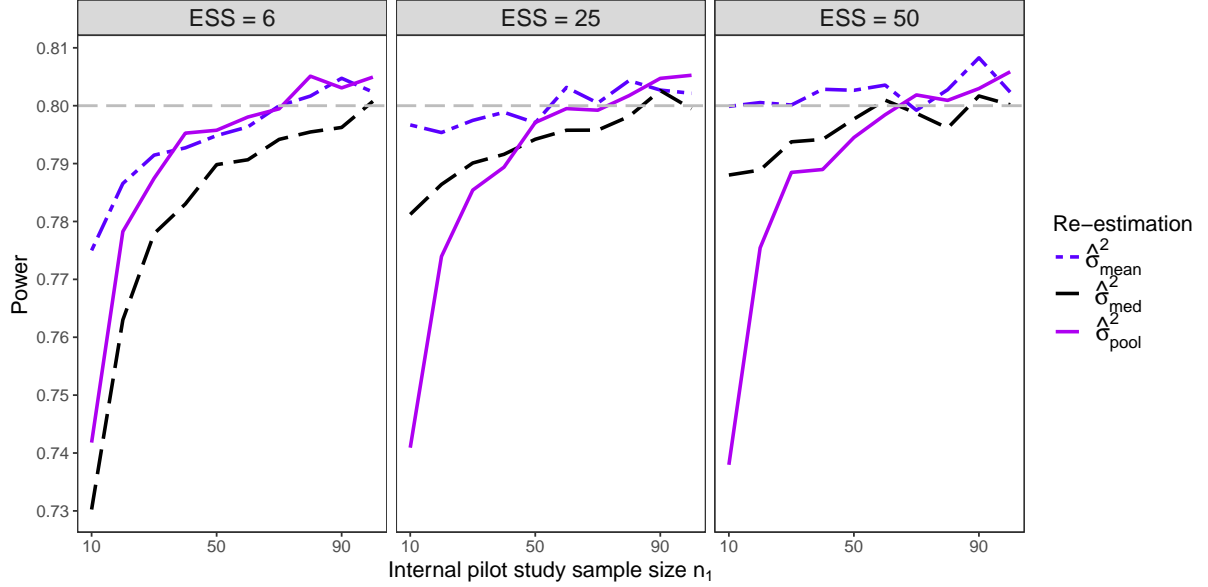


Figure 3: Power of the different sample size re-estimation procedures for effective prior sample sizes of $ESS = 6, 25, 50$. The expected value of the prior information is identical to the true variance $\sigma^2 = 1$, thus, no prior data conflict is present. The horizontal grey line depicts the nominal power of 80%.

data conflicts are present, incorporating external data into the sample size re-estimation results in a power closer to the nominal level compared to the traditional sample size re-estimation approach. A sample size re-estimation based on the posterior mean $\hat{\sigma}_{1,mean}^2$ leads to better results than the re-estimation based on the posterior median $\hat{\sigma}_{1,med}^2$. This is due to the equality of the prior mean and true variance as well as the fact that the prior median is slightly smaller than the prior mean for the considered scenarios. Moreover, the larger the effective prior sample size, the smaller is the internal pilot study sample size required to reach to the nominal level. In Figure 4 the distribution of the final sample size \hat{n}_{final} , depicted by the median and the range between the 10% and 90% percentile, is compared between the traditional sample size re-estimation procedure and the procedure incorporating prior information. We do not present the results for the re-estimation procedure based on the posterior median since the results are qualitatively the same as for the procedure based on the posterior mean. Figure 4 shows that the distribution of the final sample size is positively skewed for both sample size re-estimation procedures. Moreover, even prior information with a small effective sample size of $ESS = 6$ results in a smaller variability of the final sample size when incorporated into the sample size re-estimation. The variability of the final sample size obtained with the re-estimation procedure which

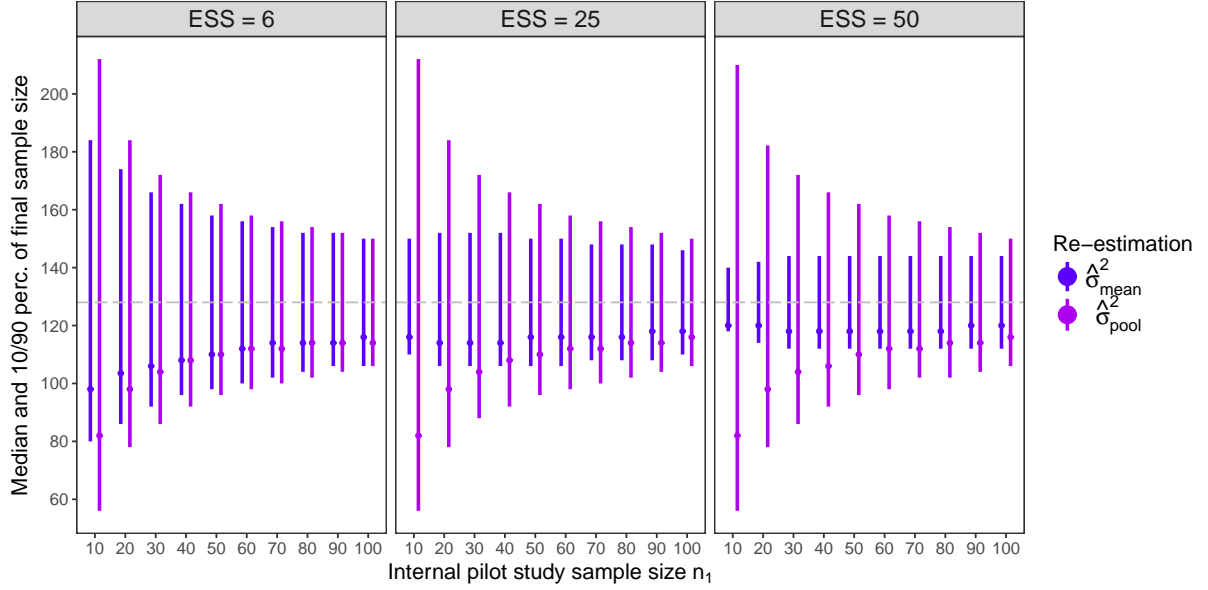


Figure 4: Median and percentiles (10% and 90%) of the final sample size. The expected value of the prior information is identical to the true variance $\sigma^2 = 1$, thus, no prior data conflict is present. The horizontal grey line depicts the fixed design sample size of $n = 128$.

incorporates prior information decreases as the effective sample size increases. The difference in variability between the sample size re-estimation procedures with and without incorporated prior information decreases as the internal pilot study sample size increases since the larger the internal pilot study sample size, the smaller the effect of the prior on the posterior distribution. In conclusion, incorporating prior information into the sample size re-estimation is beneficial when no prior data conflict is present.

Next, we study how a prior data conflict affects the performance of the sample size re-estimation procedure when the prior data is incorporated into the sample size re-estimation. Thereto, we still consider a true variance of one, $\sigma^2 = 1$, but now the parameters of the prior density $p_{\sigma^2}(\cdot)$ are chosen such that the prior distribution has an expected value of $\sigma^2_{\text{mean}} = 0.49$. The results of the corresponding Monte Carlo simulation study are presented in Figure 5. Figure 5 shows that sample size re-estimation incorporating prior data conflicting with the actual data results in underpowered trials if the prior distribution has a mean or median smaller than the true variance. Even for a small effective prior sample size of $ESS = 15$, large internal pilot studies cannot correct the effect of a prior data conflict. The underpowering increases as the effective sample size increases but decreases as the internal pilot study sample size increases. If the prior distribution would have a mean or median larger than the true variance, the sample size re-estimation incorporating prior data would overpower the clinical trial. Thus, the sample size re-estimation procedure incorporating prior information using the MAP prior does not meet the basic performance requirement when the prior data is in conflict with the variance of the ongoing clinical trial.

For the last part of this simulation study, we robustify the MAP prior as introduced above and assess whether the corresponding sample size re-estimation procedure incor-

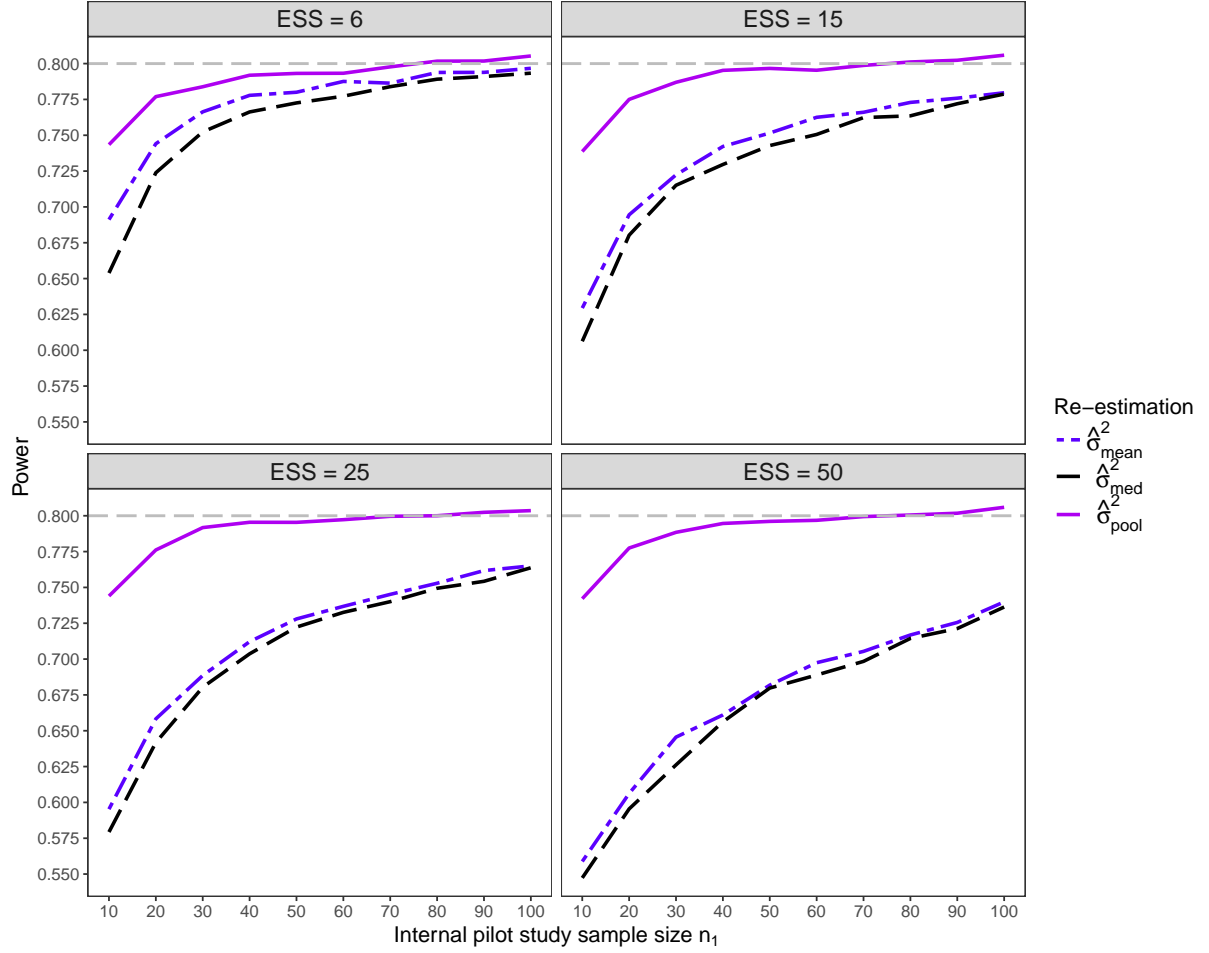


Figure 5: Power of the different sample size re-estimation procedures for effective prior sample sizes of $ESS = 6, 15, 25, 50$. The prior is in conflict with the data in the sense that the prior has an expected value of 0.49 while the true variance is $\sigma^2 = 1$. The horizontal grey line depicts the nominal power of 80%.

porating prior information is robust against prior data conflicts. We assume that the MAP prior $p_{\sigma^2}(\cdot)$ on the variance has an expected value of $\hat{\sigma}_{mean}^2 = 0.49$ while the true variance is $\sigma^2 = 1$. For the robustification we mix the MAP prior $p_{\sigma^2}(\cdot)$ with a vague prior $p_V(\cdot)$ which follows an inverse Gamma distribution with shape parameter $a = 2$ and rate parameter $b = 1$. Thus, the robustified MAP prior of the precision is given by

$$w_R \text{Gamma}(2, 1) + (1 - w_R) \text{Gamma}(ESS/2, 0.49(ESS/2 - 1)). \quad (3)$$

Moreover, the prior probability of a data conflict, w_R , is varied within the simulation study between 0.05 and 0.95. A small value of w_R corresponds to a small prior probability of a prior data conflict. Here, we focus on the results for an internal pilot study size of $n_1 = 60$ which corresponds to about half the sample size required in the fixed sample design. The effective sample size of the informative part of the robustified prior, $p_{\sigma^2}(\cdot)$, is set to $ESS = 25, 50$. The results of the power simulation are shown in Figure 6. More detailed simulation results in which the internal pilot study size is varied too and more effective sample sizes are considered are shown in Figure 1 in the Supplementary

Material. Figure 6 shows that the larger the prior probability of a prior data conflict,

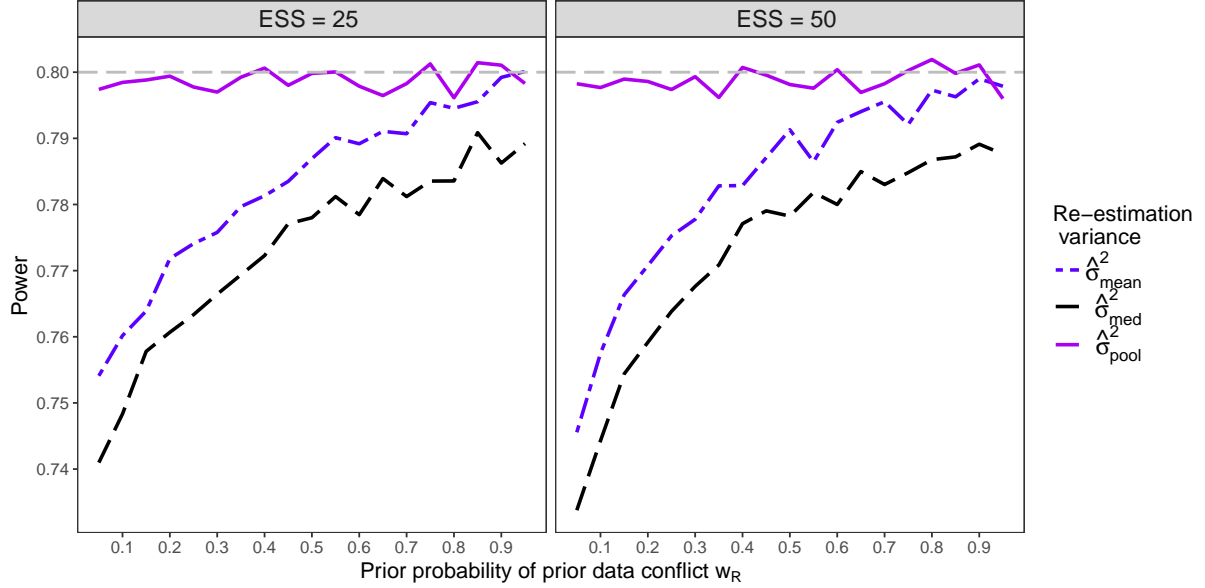


Figure 6: Power of the different sample size re-estimation procedures when the prior is robustified and a prior data conflict is present. The sample size of the internal pilot study is $n_1 = 60$. The horizontal grey line depicts the nominal power of 80%.

the less does the prior data conflict affect the power of the final analysis after sample size re-estimation. However, Figure 6 also shows that the prior probability w_R for a data conflict has to be very close to one in the case of a prior data conflict to mitigate the effects of a prior data conflict on the power. Moreover, an increase of the prior probability w_R also reduces the benefits of incorporating external information into the sample size re-estimation when no prior data conflict is present as the results presented in Figures 2 and 3 in the Supplementary Material highlight.

Robustifying the MAP prior does not result in the desired power of the sample size re-estimation procedure for the case of a prior data conflict because the information from the internal pilot study cannot appropriately discount the prior information. We will illustrate the inability of the internal pilot study to discount incorrect prior information further in the following. Thereto, we assume an observed pooled variance of one from the internal pilot study, i.e. $\hat{\sigma}_{1,pool}^2 = 1$. The prior information on the variance is the same as the mixture in Formula (3). In Figure 7 the posterior mean of the variance is plotted against the prior probability w_R of a prior data conflict for the prior effective sample sizes $ESS = 25, 50$ as well as the internal pilot study sizes $n_1 = 25, 50, 75$. Figure 7 shows only a large prior probability w_R of a data conflict results in discounted prior information. The larger the internal pilot study sample size, the more the prior information is discounted for a fixed prior probability w_R . Moreover, a larger prior effective sample size can also be beneficial in detecting a prior data conflict. However, for the considered practically relevant effective sample sizes and internal pilot study sizes the prior information cannot be discounted enough to not reduce the power of the sample size re-estimation procedure incorporating prior information in the case of a prior data conflict.

Concluding, incorporating prior information into the sample size re-estimation results

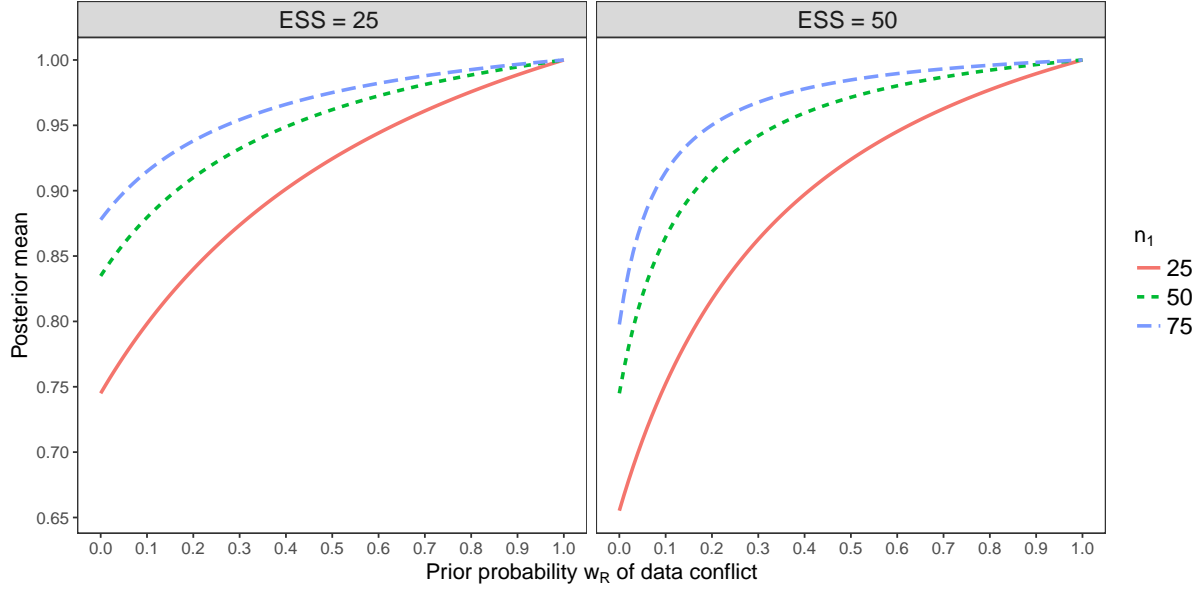


Figure 7: Posterior mean of the variance when the pooled variance estimator from the internal pilot study is equal to one, $\hat{\sigma}_{1,pool}^2 = 1$.

in a power closer to the target power compared to the sample size re-estimation based on the pooled variance estimator in the case of no prior data conflict. Moreover, the variability of the final sample size also decreases when correct prior information are incorporated into the sample size re-estimation. However, when the prior data conflicts with the data of the internal pilot study, incorporating external information into the sample size re-estimation leads to under- or overpowered clinical trials. The adverse influence of a prior data conflict can be limited, but not corrected, by robustifying the prior information which, however, reduces the benefit of incorporating prior information into the sample size re-estimation in the case of no prior data conflict.

6 Blinded sample size re-estimation

In this section we discuss various ways of incorporating prior information into the blinded sample size re-estimation and we outline why the resulting procedures face the same obstacles as the unblinded procedures in the case of a prior data conflict. The one-sample variance estimator, which estimates the unknown variance by the sample variance of the blinded data, is the recommended method for sample size re-estimation in two-arm trials with continuous data.^[22] In contrast to sample size re-estimation based on the unbiased pooled sample variance, sample size re-estimation based on one-sample variance estimator meets the target power due to overestimating the outcome variance. The relationship between the one-sample variance estimator $\hat{\sigma}_{OS}^2$ and the pooled sample variance can be illustrated by the following equation^[31]

$$\hat{\sigma}_{OS}^2 = \frac{n_1 - 2}{n_1 - 1} \hat{\sigma}_{pool}^2 + \frac{n_{1T} n_{1C}}{n_1 (n_1 - 1)} (\bar{X}_{1T} - \bar{X}_{1C})^2.$$

Since simply replacing the pooled variance estimator with the one-sample variance estimator resulted in the desired properties of the sample size re-estimation, it seems natural to proceed similar when incorporating prior information into the sample size re-estimation. Thus, when updating the prior information on the variance the pooled sample variance could be replaced by the one-sample variance estimator. Doing so increases the power of the sample size re-estimation procedure incorporating prior information. In simulations not presented here we observed that in the case of a prior data conflict the power increase is small compared to the deviations to the target power and that the prior information are not discounted enough to actually obtain a suitable procedure for incorporating prior information into the sample size re-estimation.

An alternative method for blinded sample size re-estimation in two-arm trials with a randomized block design is based on the Xing-Ganju variance estimator which estimates the outcome variance blinded based on the block sums.^[32] Sample size re-estimation incorporating prior information can be extended to not require unblinding by focusing on the likelihood of the block sums when updating the prior information. In more detail, let b be the number of randomized blocks and let m be the number of observations within each block. For the sake of simplicity, we assume equal allocation between treatment arms within each block. Conditioned on the means μ_T and μ_C and the variance σ^2 , the block sums T_i , $i = 1, \dots, b$, are normally distributed,

$$T_i | \mu_T, \mu_C, \sigma^2 \sim \mathcal{N}(0.5m(\mu_T + \mu_C), m\sigma^2).$$

Thus, $S_i = T_i/\sqrt{m}$ follows conditionally a normal distribution with mean $0.5\sqrt{m}(\mu_T + \mu_C)$ and variance σ^2 . In Section 3 we considered improper uniform priors for the means. From this assumption follows that the prior for the sum of means is also an improper uniform prior. The formulas for updating a Gamma mixture prior for the precision can be easily adapted from Section 3 by using the Xing-Ganju estimator

$$\hat{\sigma}_{XG}^2 = \frac{1}{b-1} \sum_{i=1}^b (S_i - \bar{S})^2$$

instead of the pooled variance estimator and noting that the degrees of freedom are $b-1$ instead of n_1-2 . That being said, the similarity of the models also implies that the performance of the resulting sample size re-estimation procedures incorporating prior information will be very similar to the case of the unblinded sample size re-estimation with prior information. The lower number of degrees of freedom of the Xing-Ganju variance estimator further reduces the ability to discount prior information in the case of a prior data conflict, too. Thus, blinded sample size re-estimation incorporating prior information based on the Xing-Ganju variance estimator will not achieve the target power.

The blinded data from the internal pilot study follow a mixture of two normal distributions. Therefore, it has been studied to estimate the variance for the blinded sample size re-estimation using the expectation-maximization (EM) algorithm.^[31,33,34] However, the variance estimator from the EM algorithm is biased downwards resulting in a sample size re-estimation procedure underpowering clinical trials. When updating the prior information on the variance after the internal pilot study using the likelihood of a mixture of normal distributions, similar effects can be observed. The posterior distribution for the variance has a mean and median smaller than the pooled variance. Thus, considering

those location parameters in the sample size re-estimation does also result in underpowering the clinical trial.

Concluding, prior information can easily be incorporated into the blinded sample size re-estimation. However, similar to the unblinded sample size re-estimation incorporating prior information, in the case of a prior data conflict the prior data cannot be discounted enough to ensure that the resulting sample size re-estimation procedure results in an clinical trial meeting the target power.

7 Discussion

In this manuscript we studied various methods for incorporating prior information on the nuisance parameter into nuisance parameter based sample size re-estimation. The prior information was given as an MAP prior which is obtained through a meta-analysis of variances from historical clinical trials using a Bayesian hierarchical model. In the case of no prior data conflict, that is when the prior mean corresponds to the true variance of the ongoing clinical trial, incorporating prior information into the sample size re-estimation decreases the variability of the final sample size distribution compared to the unblinded sample size re-estimation based on the pooled sample variance. Moreover, in contrast to the unblinded sample size re-estimation procedure, the sample size re-estimation procedure incorporating prior information meets the nominal power when the prior information is correct. However, the sample size re-estimation approach incorporating prior information is not robust to prior data conflicts which leads to under- or overpowered clinical trials when the variance of the ongoing trial differs from the historically observed variances. Robustifying the MAP prior does improve the performance of the sample size re-estimation approach incorporating prior data, however, not to the point where the clinical trials are not under- or overpowered. This is due to the internal pilot studies not containing enough information to discount the misspecified prior information of the nuisance parameter. The performance of sample size re-estimation incorporating prior information was primarily studied for unblinded data even though blinded sample size re-estimation is in general recommended. That being said, we proposed several approaches to incorporate prior information into the blinded sample size re-estimation and we exemplified that the resulting blinded sample size re-estimation procedures incorporating prior information do not meet the target power either when a prior data conflict is present. Concluding, incorporating prior information into the nuisance parameter based sample size re-estimation can be beneficial in the sense that it reduces the variability of the re-estimated sample size compared to the sample size re-estimation without prior information. However, incorporating prior information into the nuisance parameter based sample size re-estimation also bears the risk of resulting in an under- or overpowered clinical trial when a prior data conflict is present. This risk is not present in the traditional nuisance parameter based sample size re-estimation which generally meets the target power.

Hartley studied blinded sample size re-estimation for normal data and concluded that incorporating prior information into the blinded sample size re-estimation is generally recommended.^[14] It is worth highlighting the differences between Hartley’s publication and our manuscript since we draw a different conclusion. In Hartley’s publication, prior information on both the variance and the effect are incorporated into the sample size re-estimation which selects the final sample size based on a predictive power. In contrast, we

did not consider uncertainty in the effect size and we studied the setting where the final sample size is determined based on the sample size formula for Student's t -test as it is common in nuisance parameter based sample size re-estimation for a frequentist analysis at the end of the clinical trial. Moreover, in this manuscript we focused on the overarching approach of both summarizing the prior information based on the MAP approach and incorporating the gathered prior information into the nuisance parameter based sample size re-estimation. We also extensively studied the case of prior data conflicts which eventually lead to our conclusion to not recommend sample size re-estimation based on prior information.

The focus of this manuscript was sample size re-estimation in the case of a two-arm parallel group superiority trial with normally distributed outcomes. While incorporating prior information into the nuisance parameter based sample size re-estimation generically cannot be recommended in this design, it might be beneficial in other designs for which nuisance parameter based sample size re-estimation has been proposed. For instance, designs with more than two treatment arms or designs with count data.^[35,36] The performance of the nuisance parameter based sample size re-estimation procedures incorporating prior information in these designs might differ due to larger internal pilot studies or endpoints for which prior data conflicts can be detected easier. Moreover, we studied incorporating prior information of the nuisance parameter based the sample size re-estimation. Others have proposed to adjust the sample size of a clinical trial based on treatment effect estimates.^[37] In future research effect-based sample size re-estimation incorporating prior information should be studied. Moreover, while we presented a re-estimation approach which adjusts the sample size by plugging in a Bayes point estimator into the sample size formula, other rules for selecting the final sample size could be chosen. For instance, decision theoretic methods could be used to derive possibly better rules for the sample size re-estimation.^[38]

The simulation and calculations presented in this manuscript were performed using the R language.^[39] To reproduce the results presented in this manuscript, the respective code has been made available through the R package *varmap*.^[40]

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